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13. ABSTRACT ***(Maximum 200 Words)***

We have studied transcription-coupled repair (TCR) and global genome repair (GGR) of UV damage in the dihydrofolate reductase gene in HCC1937 cells. HCC1937 is a human breast cancer cell line that has mutations in BRCA1. We found no defect in the removal of UV-induced cyclobutane pyrimidine dimers. Hence, we and others find no evidence for a linkage between defects in either BRCA1 or BRCA2 and reduced repair of "bulky adducts." We have now focused our attention on the construction of inducible expression systems to regulate DNA repair proteins in different genetic backgrounds. Nucleotide excision repair (NER) is the major pathway in humans for the removal of UV photoproducts. In addition it removes a wide variety of bulky lesions formed by chemical agents including carcinogens. Hence mutations or polymorphisms in NER genes could be associated with an increased risk of breast cancer if a reduction in the removal of carcinogens is involved in the etiology of breast cancer. We have constructed expression vectors containing wild type or polymorphic alleles of the XPA gene and independently introduced them into an XPA deficient cell line. TCR, GGR and cell survival following UV-irradiation were studied in each cell line.

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Introduction

Nucleotide excision repair (NER) is the major pathway in humans for the removal of cyclobutane pyrimidine dimers (CPDs) and 6-4 photoproducts produced by ultraviolet light [1]. NER also removes a wide variety of bulky lesions formed by chemical agents. It is a complex multi-step process that requires the participation of at least 30 proteins [2, 3] and involves damage recognition, unwinding of the DNA helix near the lesion, dual incisions (one on each side of the lesion), removal of a stretch of DNA containing the lesion, resynthesis of DNA to replace the damaged DNA and ligation. There are two subpathways in NER [4]: one is termed transcription-coupled repair (TCR) which selectively removes lesions from the transcribed strands of expressed genes and the other is global genome repair (GGR) which removes lesions from the remainder of the genome. CPDs and 6-4 photoproducts are substrates for both subpathways of NER [5] but 6-4 photoproducts are removed more rapidly than CPDs from most of the genome [6, 7].

Xeroderma pigmentosum (XP) is a rare genetic disease with an autosomal recessive mode of inheritance [8-11]. Patients are extremely sensitive to sunlight and display freckling and other pigmentation abnormalities in sun exposed areas of the skin. One of the hallmarks of the disease is a 1000 fold increase in the frequency of skin cancer [12]. In addition, some patients develop internal tumors. XP is genetically complex with eight complementation groups; seven are defective in NER (XPA to XPG) and one is defective in translesion DNA synthesis at UV photoproducts (XPV) [13]. The etiology of the high frequency of cancer associated with the disease is based on the reduced ability to process DNA damage, which results in an increased mutational load and neoplastic transformation.

The inheritance of two mutant alleles of an XP gene can highly predispose humans [9, 12] and mice [14-18] to cancer. While XP genes play a crucial role in protecting against sunlight-induced skin cancers, their protective role against non-cutaneous tumors in humans is difficult to evaluate but XP patients below the age of 20 exhibit a 10-20 fold increase in internal cancers [19]. In contrast, XP mutations in mice clearly confer an increase in internal cancers and produce elevated frequencies of benzo[a]pyrene-induced lung tumors [20], 2-acetylaminofluorene-induced liver and lung tumors and spontaneous testicular tumors [21]. It is controversial as to whether human carriers of a single mutant allele are in fact predisposed to cancer but there is evidence that family members of XP patients may be at greater risk for developing skin cancer [22]. There are also reports of diminished repair and increased chromosomal instability in XP carriers [23-27], but others find no evidence for diminished repair [28]. Perhaps the investigation of larger numbers of XP families and the implementation of more sensitive repair assays will help resolve the question of whether XP carriers have reduced repair capabilities or are predisposed to cancer. In contrast to human heterozygotes, *XPC+/-* mice are clearly predisposed to cancer [16]. The differences between rodent and human studies could be related to the rarity of the disease in humans and the inability to experiment on human subjects.

Polymorphisms in XP genes could contribute to defects in nucleotide excision repair in the general population and increase susceptibility for skin and non-cutaneous cancers [29, 30]. DNA repair capabilities vary among individuals and in at least some individuals, these variations may have a genetic basis [31]. Polymorphisms in several XP genes have been identified [30, 32-39]. Polymorphisms in the *XPD* gene confer a decrease in the repair of X-ray-induced [36] and UV-induced damage [40] and have been associated with basal cell carcinoma [41, 42] and possibly associated with glioma [43]. However, the functional or biological significance of most XP gene polymorphisms is largely unknown.

Most XPA patients are highly predisposed to cancer and their cells are often completely deficient in both GGR and TCR of UV damage and are extremely sensitive to killing by UV-irradiation. Therefore, polymorphisms in this NER gene may have a more measurable impact on function. We have constructed expression vectors containing wild type or polymorphic alleles of the XPA gene and independently introduced them into an XPA deficient cell line. TCR, GGR and cell survival following UV-irradiation were studied in each cell line.

Body

A plasmid containing the complete *XPA* cDNA cloned into pET16B was provided by Dr. Kiyoji Tanaka (Osaka University) and it was used to construct the plasmids pIND-XPAwt (wild type *XPA*), pIND-R228Q (*XPA* with the Arg to Gln change at codon 228) and pIND-V234L (*XPA* with the Val to Leu change at codon 234). It was first digested with *Nde*I, then treated with Klenow fragment to fill in the *Nde*I ends, digested with *Bam*H1 and the *XPA* cDNA containing restriction fragment purified by gel electrophoresis. This fragment was cloned into the ecdysone hormone inducible expression vector pIND (InVitrogen) after pIND was first digested with *Afl*II, then treated with Klenow to fill in the *Afl*II-generated ends and subsequently digested with *Bam*H1. The resulting clone pIND-XPAwt was sequenced to confirm that this strategy resulted in the introduction of a Kozak sequence near the first codon of the *XPA* gene and that the plasmid retained the correct sequence of wild type *XPA*. To construct polymorphic *XPA* alleles identified in this study, site directed mutagenesis of pIND-XPAwt was performed using the Unique Site Elimination (U.S.E.) kit according to the manufacturer's instructions (Amersham Pharmacia, Piscataway, NJ) with the exception that incubations with DNA polymerase were performed at 40^0C. The primer mut228, 5'gaattgcgg**caa**gcagtaagaagc3', was used to create the R to Q change at codon 228 and the primer mut234, 5'gtaagaagcagc**ttg**tggaaaagg3', was used to create the V to L change at codon 234. Sequencing confirmed that the resulting plasmids, pIND-R228Q and pIND-V228L, contained the correct mutations and had not acquired additional mutations elsewhere. The following primers were used for sequencing: (1) ecdysone forward primer and BGH reverse primer, both from InVitrogen, were used to sequence the 5' and 3' ends of the XPA gene insert and (2) XPAint (5'atgcgaagaatgtggga3') and XPAintR

(5'cacagtctttcagaagat3') were used to sequence the central region of the XPA gene insert.

The Ecdysone Inducible Mammalian Expression System (Invitrogen) was used to establish stable XP12RO-SV cell lines containing the plasmids pIND-XPAwt, pIND-R228Q or pIND-V234L. This system relies on transfection with two different vectors: pVgRXR and pIND containing wild type or variant *XPA* cDNA. The plasmid pVgRXR contains genes encoding the Drosophila ecdysone receptor and the mammalian RXR gene, which together form a functional ecdysone receptor capable of promoting transcription from ecdysone response elements. XP12RO cells (1×10^6) were transfected with 10 μg of each plasmid by electroporation using Gene Pulser (Bio-Rad, Richmond, CA). Stable transfectants were selected in growth medium containing 400 μg/ml Zeocin and 400 μg/ml G418. Four stable cell lines were established and used in this study: RXR (XP12RO-SV transfected with pVgRXR alone), XPAwt (XP12RO-SV transfected with pVgRXR and pIND-XPAwt), R228Q (SV40-SV transfected with pVgRXR and pIND-R228Q) and V234L (SV40-SV transfected with pVgRXR and pIND-V234L).

The relative abundance of XPA protein in the cell lines described above was determined by immunoblotting using mouse monoclonal antibodies to human XPA. Cells were lysed in buffer containing 12.5 mM Tris-HCL (6.8), 2% SDS, 2% β-mercaptoethanol, 20% glycerol, and bromophenol blue. Equal amounts of protein were boiled for 3-5 minutes, separated by electrophoresis in SDS/12% PAGE gels, and electroblotted to nitrocellulose membranes. The membranes were briefly allowed to dry and then incubated overnight with 1X PBS, 0.1% Tween-20, and 7% nonfat dry milk. Immunoblotting was performed by addition of mouse monoclonal antibodies to human XPA (Neomarkers, Fremont, CA 400X dilution) and incubation for an additional 1.5 hrs. Membranes were then washed with 1X PBS and 0.1% Tween-20 and incubated with horse radish peroxide-conjugated goat anti-mouse horseradish peroxidase antibodies (5000X dilution, Sigma, St. Louis, MO) for 1.5 hrs. After several washes in 1X PBS and 0.1% Tween-20, antibody binding to XPA was detected using enhanced chemiluminescence (Amersham). Membranes were then incubated with polyclonal antibodies to actin (1000X dilution, Sigma) and horseradish peroxidase-conjugated anti-rabbit antibodies to detect the relative abundance of actin in each sample.

The removal of CPDs from the transcribed or nontranscribed strand of a 20kb *Kpn*I restriction fragment that resides within the transcription unit of the dihydrofolate reductase gene was examined as described [44]. Cells were irradiated with UV light (10 J/m^2) and either lysed immediately or incubated for increasing periods of time to allow repair and then lysed. For experiments examining the effects of XPA induction, the ecdysone hormone analog, ponasterone A, was added to the growth medium 24 h prior to UV irradiation and for the specified periods of time following UV-irradiation. DNA was isolated,

treated with *Kpn*I, mock-treated or treated with T4 endonuclease V to produce a single-strand DNA break at each CPD, electrophoresed under denaturing conditions, transferred to a membrane and sequentially hybridized with strand-specific probes. The ratio of full length restriction fragments in the T4 endonuclease V treated and untreated samples was determined by scanning densitometry of the autoradiograms and used to determine the average number of CPDs per fragment.

The removal of CPDs and 6-4 photoproducts from total genomic DNA was measured using an immunoblot assay as described [7] with some modifications. Cells were irradiated with UV light (10 J/m^2) and either lysed immediately or incubated for increasing periods of time to allow for repair and then lysed. For experiments examining the effects of XPA induction, ponasterone A was added to the growth medium 24 h prior to UV irradiation and for the specified periods of time following UV-irradiation. DNA was isolated, denatured and an equal amount from each sample was fixed to a Hybond nytrocellulose membrane (Amersham) using a slot blot apparatus (250 ng of DNA per slot for detection of 6-4 photoproducts and 25 ng of DNA per slot for detection of CPDs). The membranes were incubated with mouse monoclonal antibodies specific for either CPDs or 6-4 photoproducts [45]. Goat anti-mouse horseradish peroxide-conjugated secondary antibodies, enhanced chemiluminescence and autoradiography were used to detect binding of the primary antibody. After detecting the relative binding of the antibodies to CPDs or 6-4 photoproducts, the relative amount of DNA in each slot was determined by incubating the membranes with a radio-labeled DNA probe made by random priming of genomic human DNA. Scanning densitometry of the autoradiograms was used to determine the relative amount of DNA bound to each slot. The relative amount of antibody bound to each slot was divided by the relative amount of DNA bound to each slot and used to calculate the percentage of 6-4 photoproducts or CPDs removed at each time point.

Cells were plated at clonal density, incubated for 24 hours, irradiated with UV doses ranging from 0 to 12 J/m^2, incubated for 10-14 days, and stained with crystal violet. Colonies were scored and surviving fractions for each dose were calculated.

Key Research Accomplishments

Ecdysone-inducible expression vectors containing wild type *XPA* cDNA or cDNAs representing the two polymorphisms that we identified in exon 6 were created and independently introduced into the *XPA* deficient cell line XP12RO-SV. Transcription-coupled repair, global genome repair and cell survival following UV-irradiation were studied in each cell line in the absence or presence of the ecdysone hormone analog, ponasterone A. No substantial difference in repair or cell survival was found in cells complemented with wild type or polymorphic alleles of *XPA*. A 10-fold increase in the expression of XPA by addition of

ponasterone A resulted in faster removal of 6-4 photoproducts from the total genomes of cells complemented with wild type or polymorphic alleles of *XPA* but had no significant impact on transcription-coupled repair or global genome repair of cyclobutane pyrimidine dimers. Hence polymorphisms in the coding region of the XPA gene do not reduce nucleotide excision repair or cell survival after UV-irradiation.

Reportable Outcomes

1. Polymorphisms in DNA Repair genes and Cancer Risk, Presented at The Mammalian DNA Repair Gordon Research Conference, Ventura CA, 2000
2. "Polymorphisms in the human xeroderma pigmentosum group A gene and their impact on cell survival and nucleotide excision repair" Mellon, I., Hock, T., Reid, R., Porter, P.C. and States, J.C. submitted *DNA Repair*

Conclusions

Two polymorphisms in the human XPA gene do not reduce repair of UV light induced damage. However, they may have an impact on the removal of bulky adducts induced by carcinogens. Experiments are being conducted to test this hypothesis.

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